PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 211/22, 211/26

A2

(11) International Publication Number: WO 95/25091

(43) International Publication Date: 21 September 1995 (21.09.95)

(21) International Application Number: PCT/US95/03145

(22) International Filing Date: 14 March 1995 (14.03.95)

(30) Priority Data:
08/213,772 16 March 1994 (16.03.94) US
08/364,896 27 December 1994 (27.12.94) US

(71) Applicant: ORTHO PHARMACEUTICAL CORPORATION [US/US]; U.S. Route #202, P.O. Box 300, Raritan, NJ 08869-0602 (US).

(72) Inventors: BEAVERS, Mary, Pat; 192 Hackberry Court, Warrington, PA 18976 (US). ANDRADE-GORDON, Patricia; 301 Windy Run, Doyletown, PA 18901 (US). HOEKSTRA, William, J.; 1125 Morris Avenue, Bryn Mawr, PA 19010 (US).

(74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson and Johnson, One Johnson and Johnson Plaza, New Brunswick, NJ 08933 (US).

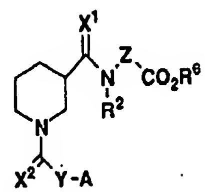
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: NIPECOTIC ACID DERIVATIVES AS ANTITHROMBIC COMPOUNDS

(57) Abstract

Nipecotic acid-derived compounds of formula (I) are disclosed as useful in treating platelet-mediated thrombotic disorders.



(I)

Nipecotic acid derivatives as antithrombic compounds

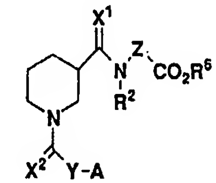
Background of the Invention

This is a continuation-in-part of application Serial No. 08/364,896, filed December 27, 1994, which application is a continuation-in-part of application Serial No. 08/213,772, filed March 16, 1994.

Platelet aggregation constitutes the initial hemostatic response to curtail bleeding induced by vascular injury. However, pathological extension of this normal hemostatic process can lead to thrombus formation. The final, common pathway in platelet aggregation is the binding of fibrinogen to activated, exposed platelet GPIIb/IIIa. Agents which interrupt binding of fibrinogen to platelet glycoprotein IIb/IIIa (GPIIb/IIIa), therefore, inhibit platelet aggregation. These agents are, therefore, useful in treating platelet-mediated thrombotic disorders such as arterial and venous thrombosis, acute myocardial infarction, unstable angina, reocclusion following thrombolytic therapy and angioplasty, inflammation, and a variety of vaso-occlusive disorders. The fibrinogen receptor (GPIIb/IIIa) is activated by stimuli such as ADP, collagen, and thrombin exposing binding domains to two different peptide regions of fibrinogen: α-chain Arg-Gly-Asp (RGD) and γ-chain His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val (HHLGGAKQAGDV, γ400-411). Since these peptide fragments themselves have been shown to antagonize (inhibit) fibrinogen binding to GPIIb/IIIa, a mimetic of these fragments would also serve as an antagonist. In fact, prior to this invention, potent RGD-based or RGD mimetic antagonists have been revealed which inhibit both fibrinogen binding to GPIIb/IIIa and platelet aggregation. Some of these agents have also shown *in vivo* efficacy as antithrombotic agents and, in some cases, have been used in conjunction with fibrinolytic therapy (e.g., t-PA or streptokinase) as well.

DISCLOSURE OF THE INVENTION

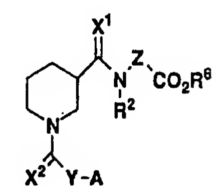
The present invention is directed to compounds represented by the following general formula (I):



wherein X^1, X^2, Y, Z, R^2 and A are as hereinafter defined. Such compounds, based upon structural features of fibrinogen γ400-411, are platelet aggregation inhibitors useful in treating platelet-mediated thrombotic disorders such as arterial and venous thrombosis, acute myocardial infarction, reocclusion following thrombolytic therapy and angioplasty, inflammation and unstable angina and a variety of vaso-occlusive disorders. These compounds are also useful as antithrombotics used in conjunction with fibrinolytic therapy (e.g., t-PA or streptokinase). Pharmaceutical compositions containing such compounds are also part of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

More particularly, the present invention is directed to compounds of the following formula (I):



wherein

X^1 and X^2 are the same or different and selected from either of H_2 or O. Preferably, each of X^1 and X^2 is O.

Y is $(CH_2)_m$, $CH(NHCOR^3)(CH_2)_m$, or $CH(NH_2)CH_2)_m$.

A is NHR^1, $C(NH)NH_2$ or a cycloalkyl ring containing a nitrogen therein which ring is selected from any of piperidin-2-yl, piperidin-3-yl, piperidin-4-yl,

pyrrolidin-2-yl and pyrrolidin-3-yl. More preferably, the ring is selected from any of piperidin-2-yl, piperidin-3-yl, or piperidin-4-yl.

Z is $(CH_2)_n$ or $CH(CO_2R^4)(CH_2)_n$. Preferably, Z is $(CH_2)_2$.

R^1 is H, alkyl, or $CH(NH)NH_2$. More preferably, R^1 is H or alkyl. Most preferably, R^1 is hydrogen

R^2 is H or alkyl. Preferably, R^2 is hydrogen.

R^3 is alkoxy or alkyl. Preferably, R^3 is t-butoxy or methyl. Most preferably, R^3 is t-butoxy.

R^4 is alkyl or arylalkyl such as benzyl. Preferably, R^4 is methyl.

R^6 is H, alkyl or arylalkyl such as benzyl. When R^6 is other than H, it is in its prodrug form.

m is the integer 0, 1, 2, or 3.

n is the integer 0, 1, or 2.

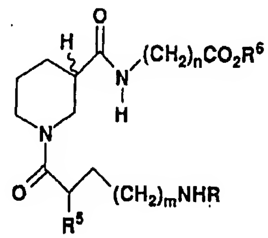
As used herein, unless otherwise noted alkyl and alkoxy whether used alone or as part of a substituent group, include straight and branched chains having 1-8 carbons. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, n-hexyl, 2-hexyl and 2-methylpentyl. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. Cycloalkyl groups contain 5-8 ring carbons and preferably 6-7 carbons.

The term "aryl" as used herein alone or in combination with other terms indicates aromatic hydrocarbon groups such as phenyl or naphthyl. The term "arylalkyl" means an alkyl group substituted with an aryl group.

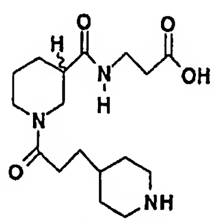
The compounds of the present invention may also be present in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salt

generally takes a form in which the nitrogen on the 1-piperidine substituent is protonated with an inorganic or organic acid. However when X^2 is H_2 the ring nitrogen may be subject to salt formation. Representative organic or inorganic acids include hydrochloric, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benezenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharic or trifluoroacetic.

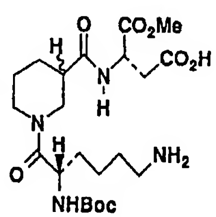
Particularly preferred compounds of the present invention include compounds represented by the formula:



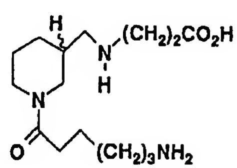
R=H m=3 n=2 R^5=L-NHBoc R^6 is benzyl (Bn) (CP #1);
R=H m=3 n=2 R^5=L-NHBoc R^6 is H (CP #2);
R=H m=3 n=2 R^5=D-NHBoc R^6 is H (CP #3);
R=H m=3 n=2 R^5=L-NH_2 R^6 is H (CP #4);
R=H m=3 n=2 R^5=H R^6 is H (CP #5);
R=H m=3 n=1 R^5=L-NHAcR^6 is H (CP #6);
R=H m=3 n=2 R^5=L-NHAc R^6 is H (CP #7);
R=C(NH)NH_2 m=2 n=2 R^5=L-NHBoc R^6 is H (CP #8);
R=H m=3 n=3 R^5=L-NHBoc R^6 is H (CP #9);
R=H m=3 n=2 R^5=D-NH_2 R^6 is H (CP #10);
R=H m=3 n=3 R^5=D-NHBoc R^6 is H (CP #11);
R=H m=3 n=1 R^5=D-NHBoc R^6 is H (CP #12);
R=H m=3 n=2 R^5=D-NHAc R^6 is H (CP #13);
3-S-isomer of CP#3 R^6 is H (CP #14);
R=i-Pr m=3 n=2 X=L-NHBoc R^6 is H (CP #15);
3-R-isomer of CP#3 R^6 is H (CP #16);



CP #17



CP #18



CP #19

The compounds of the invention may be prepared from commercially available starting materials by the following reaction schemes AA, AB, AC and AD.

The compounds of the invention where X^1 and X^2 are each oxygen may be prepared by following scheme AA. In this scheme nipecotic acid (either the racemic mixture or either separate enantiomer) may be treated with a lower alkyl alcohol and a catalytic amount of an acid from about room temperature to reflux, to give the ester derivative <u>AA1</u> as the acidic salt. Typical alcohols which include ethanol, methanol, isopropanol and butanol may be paired with acidic catalysts such as <u>p</u>-toluenesulfonic acid, HCl or sulfuric acid. The preferred reagents are methanol and HCl. Derivative <u>AA1</u> may be acylated at the ring nitrogen with a variety of acylating agents to give derivative <u>AA2</u>. Typical reaction conditions include treating <u>AA1</u> with the acylating agent and an equivalent of an organic base in an inert solvent at room temperature for 15 min to 2 h. The preferred acylating agents are amino protected amino acids or amino protected aminoalkyl carboxylic acids, which are activated with coupling reagents such as DCC (1,3-dicyclohexylcarbodiimide) and BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride). However, amino protected acid derivatives such as anhydrides, N-oxysuccinimides, and acid chlorides may also be used. Suitable protecting groups include lower alkyl carbamates, branched alkyl carbamates, benzyl carbamates, acetamides, and substituted acetamides. The choice of acylating agent and its amino protecting group(s) is the factor that determines substituents Y and R^1 in the compounds of Formula I where X^1 and X^2 are O. In Scheme AA, the protected amino acid is the diamino acid of the formula $NH(Boc)CHCO_2H(CH_2)_nN(Cbz)$, which allows for selective deprotection of the two amino groups at a latter point in the scheme. This choice is only meant to illustrate the invention and not to limit it.

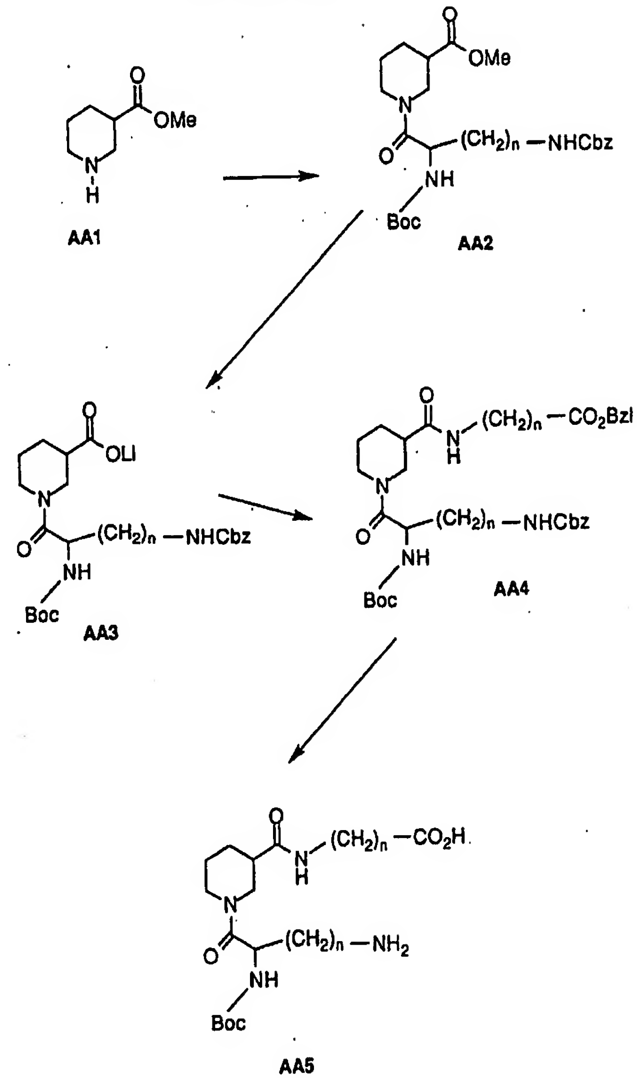
Derivative <u>AA2</u> can be treated with a base and a suitable solvent mixture to give the salt derivative <u>AA3</u>. Suitable inorganic bases include NaOH, KOH, $Mg(OH)_2$, LiOH , Na_2CO_3 and $NaHCO_3$, which may be combined with mixtures of THF and water at room temperature for 1-6 h to give the desired product. The organic bases which may be used include triethylamine, tributylamine, diisopropylethylamine and tetramethylguanidine. These bases

can be used with organic solvents at room temperature to reflux for 1-6 h to give salt AA3.

The preferred reaction conditions (which are illustrated) are the treatment of AA2 with LiOH, water and THF at room temperature for 1 h. Other suitable inorganic basis may be used such as NaOH, KOH, $Mg(OH)_2$, $NaCO_3$ and $NaHCO_3$. Should another such base be used, the Li in AA3 would, of course, be replaced by the appropriate metal substituent. Derivative AA3 may be treated with a carboxy protected carboxyalkylamine or a carboxy protected amino acid under standard amino acid coupling conditions to give the disubstituted nipecotic derivative AA4. Acceptable coupling conditions include employing peptide coupling agents such as DCC, BOP-Cl and EDC (ethyl dimethylaminopropylcarbodiimide • HCl). Suitable carboxy protecting groups include benzyl carbamates, substituted benzyl carbamates, alkyl carbamates and branched alkyl carbamates where the choice of protecting group is obvious to those skilled in chemical synthesis. The illustrated example uses $NH_2(CH_2)_nCO_2$-(Bzl) as the protected amino acid. Once again the choice of amino acid and its carboxy protecting group determine substituents R^2 and Z in the compounds of Formula I where X^1 and X^2 are O. Derivative AA4 may be selectively deprotected in accordance with the the requirements of the amino or carboxy protecting group. In the illustrated example, the protecting groups on the 3-carboxy group and one of the amino groups are simultaneously removed by catalytic hydrogenation using Pd/C in a H_2 atmosphere to give derivative AA5.

[DIP-J Classic の試用モードでダウンロードされました]

SCHEME AA

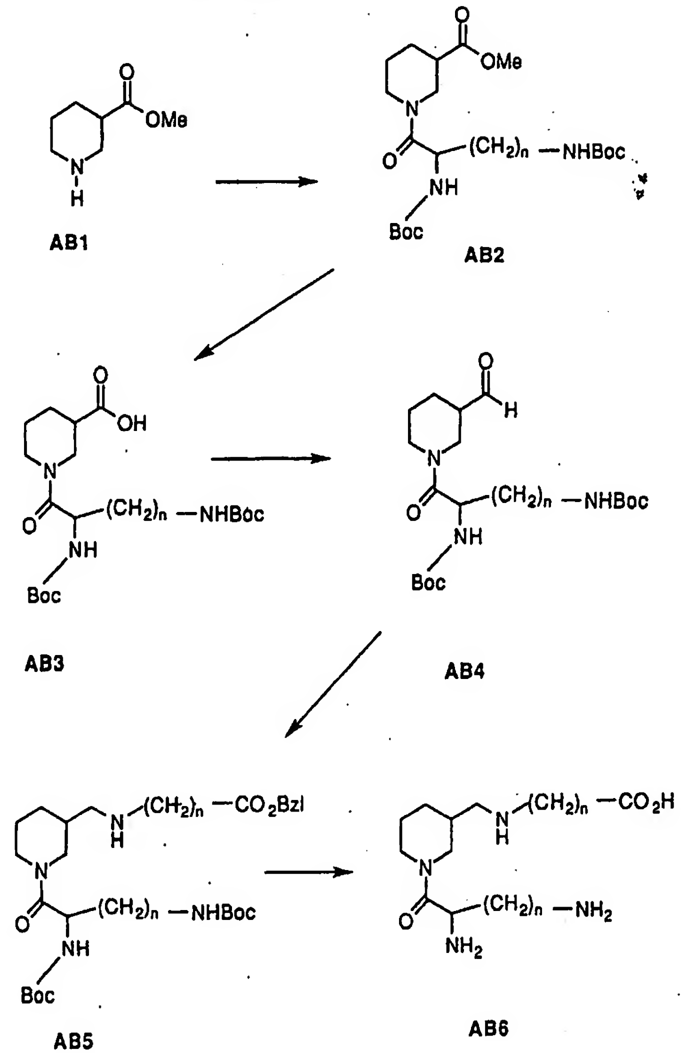


Scheme AB illustrates the preparation of compounds of Formula I where X^2 is O and X^1 is H_2 Nipecotic acid (either the racemic mixture or either separate enantiomer) may be treated with a alkyl alcohol and a catalytic amount of an acid from about room temperature to reflux, to give the ester derivative <u>AB1</u> as the acidic salt. Typical alcohols include ethanol, methanol, isopropanol and butanol. The acid catalysts include p-toluenesulfonic acid, HCl and sulfuric acid where the preferred reagents are methanol and HCl. Derivative <u>AB1</u> may be acylated at the ring nitrogen with a variety of acylating agents to give derivative <u>AB2</u>. Typical reaction conditions include treating <u>AB1</u> with the acylating agent and an equivalent of an organic base in an inert solvent at room temperature for 15 min to 2 h. The preferred acylating agents are amino protected amino acids or amino protected aminoalkyl carboxylic acids, which are activated with coupling reagents such as DCC (1,3-dicyclohexylcarbodiimide) and BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride). However, amino protected acid derivatives such as anhydrides, N-oxysuccinimides and acid chlorides may also be used. Suitable protecting groups include lower alkyl carbamates, branched alkyl carbamates, benzyl carbamates, acetamides, and substituted acetamides. The choice of amino acid and its amino protecting group(s) is the factor that determines substituents Y and R^1 in the compounds of Formula I. In Scheme AB, the protected amino acid is the diamino acid of the formula $NH(Boc)CHCO_2H(CH_2)_nN(Boc)$, this choice is only meant to illustrate the invention and not to limit it. .Derivative <u>AB2</u> can be hydrolyzed with a base and a suitable solvent mixture to give derivative <u>AB3</u>. Suitable inorganic bases include NaOH, KOH, $Mg(OH)_2$, LiOH , Na_2CO_3 and $NaHCO_3$, which may be combined with mixtures of THF and water at room temperature for 1-6 h to give the desired product. The organic bases which may be used include triethylamine, tributylamine, diisopropylethylamine and tetramethylguanidine. These bases can be used with organic solvents at room temperature to reflux for 1-6 h to give <u>AB3</u>. The 3-carboxy group of derivative AB3 may be reduced to give the aldehyde derivative <u>AB4</u> by using a number of reaction condidtions. Those conditions include the use of lithium t-diisopropylamide with HMPT/THF as a solvent from -78 to 0 °C, N,N-dimethylchloromethyleniminium chloride and lithium t-butoxyaluminum hydride with pyridine as a solvent at -78 °C and standard Rosenmund reduction conditions. The preferred reaction conditions use N,N'-carbonyldiimidazole followed by diisobutylaluminum hydride at -10 °C to give

【DIP-J Classic の試用モードでダウンロードされました】

the aldehyde derivative <u>AB4</u>. <u>AB4</u> may be treated with a carboxy protected carboxyalkylamine or a carboxy protected amino acid followed by a reducing agent to give the disubstituted nipecotic derivative <u>AB5</u>. Suitable carboxy protecting groups include benzyl carbamates, substituted benzyl carbamates, lower alkyl carbamates and branched alkyl carbamates where the choice of protecting group is obvious to those skilled in chemical synthesis. Reducing agents include sodium cyanoborohydride, lithium cyanoborohydride, sodium-9-cyano-9-hydrido-borabicyclo[3,3,1] nonane, tetrabutylammonium cyanoborohydride and Pd/C with an acidic solvent where the choice of reducing agent is determined by the protecting groups in use. The illustrated example uses $NH_2(CH_2)_nCO_2Bzl$ as the protected amino acid and sodium cyanoborohydride as a reducing agent. This choice of amino acid and its carboxy protecting group determine substituents R^2 and Z in the compound and is meant to be illustrative not limiting. Derivative <u>AB5</u> may be selectively deprotected in accordance with the the requirements of the amino or carboxy protecting group. As illustrated example, the protecting groups on the 3-carboxy group and both amino groups are simultaneously removed by catalytic hydrogenation using Pd/C in a H_2 atmosphere to give derivative <u>AB6</u>.

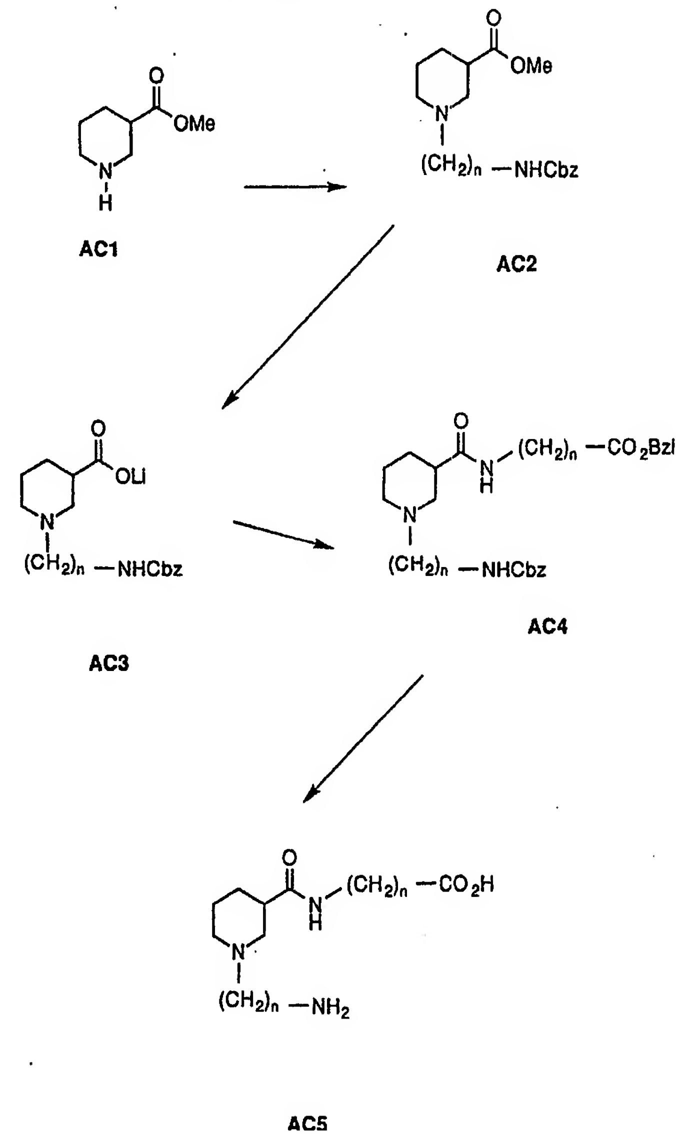
SCHEME AB



The compounds of the invention where X^1 is oxygen and X^2 is H_2 and may be prepared by following scheme AC. In this scheme nipecotic acid (either the racemic mixture or the separated enantiomers) may be treated with a lower alkyl alcohol and a catalytic amount of an acid from about room temperature to reflux, to give the ester derivative AC1 as the acidic salt. Typical alcohols include ethanol, methanol isopropanol and butanol. The acid catalysts include p-toluenesulfonic acid, HCl and sulfuric acid.with methanol and HCl as the reagents of choice.. Derivative AC1 may be alkylated at the ring nitrogen with an alkylating agent to give derivative AC2. Alkylating reagents include haloalkylamine synthons such as bromoalkylphthalimides and bromoalkylnitriles, or protected aminoaldehydes via reductive amination procedures (for conditions, see Scheme AD). Typical reaction conditions include treating AC1 with a base such as sodium hydride or a phase transfer catalyst such as tetrabutylammonium fluoride and an alkylating agent in an inert solvent at room temperature for 15 min to 2 h followed by routine protection of the 3-substituent's amino group with any of the aforementioned suitable protecting groups. The choice of alkylating agent and its amino protecting group is the factor that determines substituents Y and R^1. In Scheme AC the 1- position is substituted with $(CH_2)NH(Cbz)$, a choice that is only meant to illustrate the invention and not to limit it. Derivative AC2 can be treated with a base and a suitable solvent mixture to give the salt derivative AC3. As in Scheme AA, Scheme AC shows the use of the preferred LiOH. However, other suitable inorganic bases include NaOH, KOH, $Mg(OH)_2$, Na_2CO_3 and $NaHCO_3$, which may be combined with mixtures of THF and water at room temperature for 1-6 h to give the desired product. The organic bases which may be used include triethylamine, tributylamine, diisopropylethylamine and tetramethylguanidine. These bases can be used with organic solvents at room temperature to reflux for 1-6 h to give salt AC3. The preferred reaction conditions (which are illustrated) are the treatment of AC2 with LiOH, water and THF at room temperature for 1 h. Derivative AC3 may be treated with a carboxy protected carboxyalkylamine or a carboxy protected amino acid under standard amino acid coupling conditions to give the disubstituted nipecotic derivative AC4. Acceptable coupling conditions include employing peptide coupling agents such as DCC, BOP-Cl and EDC (ethyl dimethylaminopropyl carbodiimide • HCl). Suitable carboxy protecting groups include benzyl carbamates, substituted benzyl carbamates, alkyl carbamates and branched alkyl carbamates where the choice of protecting

group is obvious to those skilled in chemical synthesis. The illustrated example uses $NH_2(CH_2)_nCO_2Bzl$ as the protected amino acid. Once again the choice of amino acid and its carboxy protecting group determine substituents R^2 and Z in the compounds of Formula I. Derivative AC4 may be selectively deprotected in accordance with the the requirements of the amino or carboxy protecting group. In the illustrated example, the protecting groups on the 3-carboxy group and the 1-amino group are simultaneously removed by catalytic hydrogenation using Pd/C in a H_2 atmosphere to give derivative AC5.

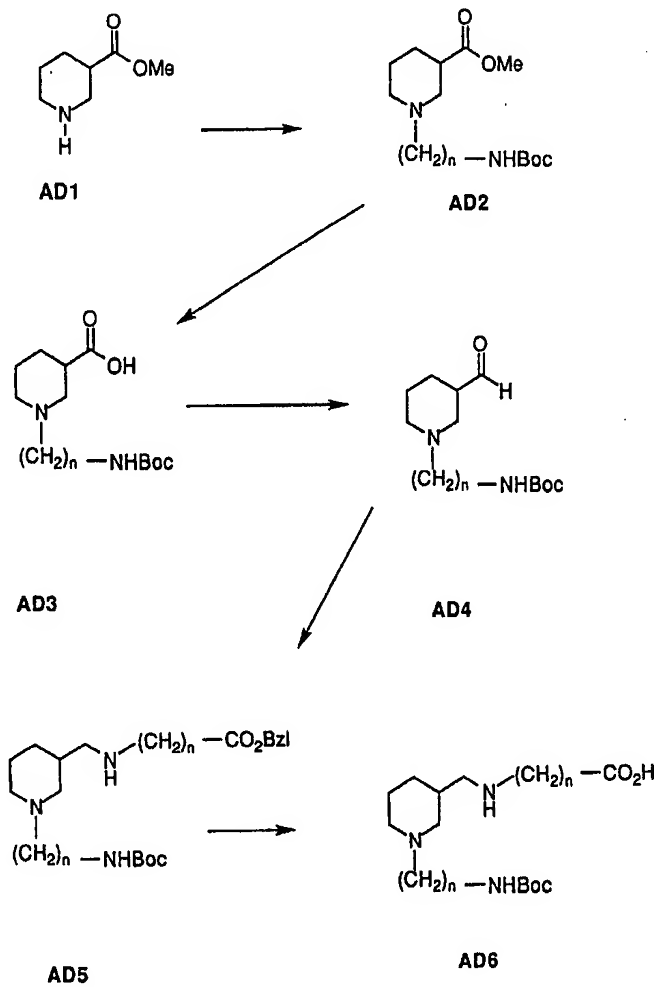
SCHEME AC



The compounds of the invention where X^1 and X^2 are each H_2 and may be prepared by following scheme AD. In this scheme nipecotic acid (either the racemic mixture or the separated enantiomers) may be treated with a lower alkyl alcohol and a catalytic amount of an acid from about room temperature to reflux, to give the ester derivative <u>AD1</u> as the acidic salt. Typical alcohols include ethanol, methanol isopropanol and butanol. The acid catalysts include
p-toluenesulfonic acid, HCl and sulfuric acid. The preferred reagents are methanol and HCl. Derivative <u>AD1</u> may be alkylated at the ring nitrogen with an alkylating agent to give derivative <u>AD2</u>. Alkylating reagents include haloalkylamine synthons such as bromoalkylphthalimides and bromoalkylnitriles, or protected aminoaldehydes via reductive amination procedures (for conditions, see Scheme AD). Typical reaction conditions include treating <u>AD1</u> with a base such as sodium hydride or a phase transfer catalyst such as tetrabutylammonium fluoride and an alkylating agent in an inert solvent at room temperature for 15 min to 2 h followed by routine protection of the amino group with any of the aforementioned suitable protecting groups. The choice of alkylating agent and its amino protecting group is the factor that determines substituents Y and R^1. In Scheme AD the 1- position is substituted with $(CH_2)NH(Cbz)$, a choice that is only meant to illustrate the invention. Derivative <u>AD2</u> can be hydrolyzed with a base and a suitable solvent mixture to give derivative <u>AD3</u>. Suitable inorganic bases include NaOH, KOH, MgOH, LiOH , Na_2CO_3 and $NaHCO_3$, which may be combined with mixtures of THF and water at room temperature for 1-6 h to give the desired product. The organic bases which may be used include triethylamine, tributylamine, diisopropylethylamine and tetramethylguanidine. These bases can be used with organic solvents at room temperature to reflux for 1-6 h to give <u>AD3</u>. The 3-carboxy group of derivative AD3 may be reduced to give the aldehyde derivative <u>AD4</u> by using a number of reaction condidtions. Conditions include the use of lithium diisopropylamide with HMPT/THF as a solvent from -78 to 0 °C, N,N-dimethylchloromethyleniminium chloride and lithium *t*-butoxyaluminum hydride with pyridine as a solvent at -78 °C and standard Rosenmund reduction conditions. The preferred reaction conditions use N,N'-carbonyldiimidazole followed by diisobutylaluminum hydride at -10 °C to give the aldehyde derivative <u>AD4</u>.

Derivative <u>AD4</u> may be treated with a carboxy protected carboxyalkylamine or a carboxy protected amino acid followed by a reducing agent to give the disubstituted nipecotic derivative <u>AD5</u>. Suitable carboxy protecting groups include benzyl carbamates, substituted benzyl carbamates, lower alkyl carbamates and branched alkyl carbamates where the choice of protecting group is obvious to those skilled in chemical synthesis. Reducing agents include sodium cyanoborohydride, lithium cyanoborohydride, sodium-9-cyano-9-hydrido-borabicyclo[3,3,1] nonane, tetrabutylammonium cyanoborohydride and Pd/C with an acidic solvent where the choice of reducing agent is determined by the protecting groups in use. The illustrated example uses $NH_2(CH_2)_nCO_2Bzl$ as the protected amino acid and sodium cyanoborohydride as a reducing agent. This choice of amino acid and its carboxy protecting group determine substituents R^2 and Z in the compound and is meant to be illustrative not limiting. Derivative <u>AD5</u> may be selectively deprotected in accordance with the requirements of the amino or carboxy protecting group. As illustrated, the protecting groups on the 3-carboxy group and the amino group are simultaneously removed by catalytic hydrogenation using Pd/C in a H_2 atmosphere to give derivative <u>AD6</u>.

SCHEME AD



AD1 AD2 AD3 AD4 AD5 AD6

With regard to starting materials for all schemes, most of the amino acids and the aminoalkylcarboxylic acids needed to produce compounds

where A is NHR1, are commercially available and only require the manipulation of protecting groups to give the desired compounds of Formula I. However, to produce the compounds of the invention where A is a cycloalkyl ring containing a nitrogen therein, the 1-substituent (piperidine) must be modified after addition to give desired compounds of Formula I. To produce the compounds where the 1-substituent is $C(O)(CH_2)_2$-4-yl-piperdine, derivatives <u>AA1</u> or <u>AB1</u> are acylated with 3-(4-pyridyl)acrylic acid to produce the acylated derivatives <u>AA2</u> and <u>AB2</u>, using the aforementioned acylation procedures. These derivatives are converted as described in the schemes to give <u>AA4</u> and <u>AB5</u>. Derivatives <u>AA5</u> and <u>AB6</u> may be produced by treating <u>AA4</u> and <u>AB5</u> with a suitable reducing agent which in this case removes the protecting group on the carboxy group of the 3-position and reduces the ethylene-substituted pyridine to give the desired compound. The preferred reducing/deprotecting agent is PtO_2. The 2 and 3-yl piperidines may be produced by modifying the acrylic acid derivative by conventional means.

To produce the compounds where the 1-substituent is $C(O)(CH_2)_2$-3-yl-pyrrole, derivatives AA1 or AB1 are acylated with 3-(1-benzylpyrrolidin-3-yl)acrylic acid to produce the acylated derivatives AA2 and AB2, using the aforementioned acylation procedures. This substituted pyrrole acrylic acid derivative may be obtained by hydrolyzing the corresponding nitrile derivative with aqueous acid. 3-(1-Benzylpyrrolidin-3-yl)acrylonitrile was synthesized according to the methods described in US Patent 4,002,643, which is incorporated herein by reference. These derivatives are treated as described above (for the six-membered case) to give the compounds of the invention where A is a five-membered ring with a nitrogen contained therein.

To produce diastereomerically-enriched final compounds which contain the Boc-D-Lys and either R- or S-nipecotyl groups (see compounds **14** and **16**), the corresponding enantiomerically-enriched nipecotic acid methyl esters were employed at the beginning of the syntheses. Enantiomerically-enriched nipecotic acid methyl esters were isolated by chiral resolution of racemic material as published (A. M. Akkerman, *Rec. Trav. Chim. Pays-Bas* **1951**, *70*, 899).

To prepare the pharmaceutical compositions of this invention, one or more compounds of formula (I) or salt thereof of the invention as the active ingredient, is intimately admixed with a pharmaceutical carrier according to

conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration, e.g., oral or parenteral such as intra muscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, through other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, of from about 0.03 mg to 100 mg/kg (preferred 0.1-30 mg/kg) and may be given at a dosage of from about 0.1-300 mg/kg/day (preferred 1-50 mg/kg/day). The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

PHARMACOLOGY

The compounds of the present invention interrupt binding of fibrinogen to platelet glycoprotein IIb/IIIa (GPIIb/IIIa) and thereby inhibit platelet aggregation. Such compounds are, therefore, useful in treating platelet-mediated thrombotic disorders such as arterial and venous thrombosis, acute myocardial infarction, reocclusion following thrombolytic therapy and angioplasty, and a variety of vaso-occlusive disorders. Because the final,

[DIP-J Classic の試用モードでダウンロードされました]

common pathway in normal platelet aggregation is the binding of fibrinogen to activated, exposed GPIIb/IIIa, inhibition of this binding represents a plausible antithrombotic approach. The receptor is activated by stimuli such as ADP, collagen, and thrombin, exposing binding domains to two different peptide regions of fibrinogen: α-chain Arg-Gly-Asp (RGD) and γ-chain 400-411. As demostrated by the results of the pharmacological studies described hereinafter, the compounds of the present invention have shown the ability to block fibrinogen binding to isolated GPIIb/IIa (IC_{50}'s 3-5800 nM), inhibit platelet aggregation *in vitro* in the presence of a various of platelet stimuli, and furthermore, have inhibited *ex vivo* platelet aggregation in animal models.

IN VITRO SOLID PHASE PURIFIED GLYCOPROTEIN IIB/IIIA BINDING ASSAY.

A 96 well Immulon-2 microtiter plate (Dynatech-Immulon) is coated with 50 μl/well of RGD-affinity purified GPIIb/IIIa (effective range 0.5-10 μg/mL) in 10 mM HEPES, 150 mM NaCl, 1 mM at pH 7.4. The plate is covered and incubated overnight at 4°C. The GPIIb/IIa solution is discarded and 150 μl of 5% BSA is added and incubated at RT for 1-3 h. The plate is washed extensively with modified Tyrodes buffer. Biotinylated fibrinogen (25 μl/well) at 2 x final concentration is added to the wells that contain the test compounds (25 μl/well) at 2 x final concentration. The plate is covered and incubated at RT for 2-4 h. Twenty minutes prior to incubation completion, one drop of Reagent A (Vecta Stain ABC Horse Radish Peroxidase kit, Vector Laboratories, Inc.) and one drop Reagent B are added with mixing to 5 mL modified Tyrodes buffer mix and let stand. The ligand solution is discarded and the plate washed (5 x 200 μl/well) with modified Tyrodes buffer. Vecta Stain HRP-Biotin-Avidin reagent (50 μl/well, as prepared above) is added and incubated at RT for 15 min.. The Vecta Stain solution is discarded and the wells washed (5 x 200 μl/well) with modified Tyrodes buffer. Developing buffer (10 mL of 50 mM citrate/phosphate buffer @ pH 5.3, 6 mg o-phenylenediamine, 6 μl 30% H_2O_2; 50 μl/well) is added and incubated at RT for 3-5 min, and then 2*N* H_2SO_4 (50 μl/well) is added. The absorbance is read at 490 nM. The results are shown in Table I.

IN VITRO INHIBITION OF THROMBIN-INDUCED GEL-FILTERED PLATELET AGGREGATION ASSAY.

The percentage of platelet aggregation is calculated as an increase in light transmission of compound treated platelet concentrate vs. control treated platelet concentrate. Blood is obtained from drug free, normal donors into tubes containing 0.13*M* sodium citrate. Platelet rich plasma (PRP) is collected by centrifugation of whole blood at 200 x g for 10 min at 25°C. The PRP (5 mL) is gel filtered through Sepharose 2B (bed volume 50 mL), and the platelet count is adjusted to 2×10^7 platelets per sample. The following constituents are added to a siliconized cuvette: concentrated platelet filtrate and Tyrode's buffer (0.14*M* NaCl, 0.0027*M* KCl, 0.012*M* $NaHCO_3$, 0.76 *mM* Na_2HPO4, 0.0055*M* glucose, 2 mg/mL BSA and 5.0*mM* HEPES @ pH 7.4) in an amount equal to 350 µl, 50 µl of 20*mM* calcium and 50 µl of the test compound. Aggregation is monitored in a BIODATA aggregometer for the 3 min following the addition of agonist (thrombin 50 µl of 1 unit/mL). The results are shown in Table I.

EX VIVO DOG STUDY

Adult mongrel dogs (8-13 kg) were anesthetized with sodium pentobarbital (35 mg/kg, I.v.) and artificially respired. Arterial blood pressure and heart rate were measured using a Millar catheter-tip pressure transducer inserted in a femoral artery. Another Millar transducer was placed in the left ventricle (LV) via a carotid artery to measure LV end diastolic pressure and indices of myocardial contractility. A lead II electrocardiogram was recorded from limb electrodes. Catheters were placed in a femoral artery and vein to sample blood and infuse drugs, respectively. Responses were continuously monitored using a Modular Instruments data aquisition system.

Arterial blood samples (5-9 ml) were withdrawn into tubes containing 3.8% sodium citrate to prepare platelet rich plasma (PRP) and to determine effects on coagulation parameters: prothrombin time (PT) and activated partial thromboplastin time (APTT). Separate blood samples (1.5 ml) were withdrawn in EDTA to determine hematocrit and cell counts (platelets, RBC's and white cells). Template bleeding times were obtained from the buccal surface using a symplate incision devise and Whatman filter paper.

Aggregation of PRP was performed using a BioData aggregometer. Aggregation of whole blood used a Chronolog impedance aggregometer. PT and APTT were determined on either a BioData or ACL 3000+ coagulation analyser. Cells were counted with a Sysmex K-1000.

Compound **17** was solubilized in a small volume of dimethylformamide (DMF) and diluted with saline to a final concentration of 10% DMF. Compound **17** was administered by the intravenous route with a Harvard infusion pump. Doses of 0.3, 1, 3, and 10 mg/kg were given in a cumulative fashion to each animal. Each dose was administered over a 15 min interval at a constant rate of 0.33 ml/min. Data were obtained after each dose and 30 and 60 min following the end of drug administration.

Compound **17** caused marked inhibition of ex vivo platelet aggregation responses. Thus, in whole blood, Compound **17** inhibited collagen-stimulated aggregation in doses of 0.3-10 mg/kg with marked inhibition of collagen stimulated platelet ATP release at 10 mg/kg. In PRP, Compound **17** also inhibited collagen stimulated platelet aggregaton with marked activity at 0.3 mg/kg. Gamma thrombin induced aggregation of PRP was inhibited at doses of 3.0 mg/kg and above. In both PRP and whole blood, platelet function began to recover within 30 - 60 min, suggesting a relatively short duration of drug action. Compound **17** had no measurable hemodynamic effect in doses up to 10 mg/kg, iv. The drug produced an increase in template bleeding time at 3 and 10 mg/kg with rapid recovery post treatment. No effects on coagulation (PT or APTT) were observed during treatment and platelet, white and RBC counts were unchanged at any dose of Compound **17**.

The results indicate that Compound **17** is a broadly effective inhibitor of platelet aggregation ex vivo (antagonizing both collagen and thrombin pathways) following iv adminnstration of doses ranging from 0.3-10 mg/kg. The antiaggregatory effect is relatively short and is accompanied by increases in bleeding time at the higher doses. No other hemodynamic or hematologic effects are observed.

TABLE I

Compound #	Binding IC_{50} (μM)	Pl. Aggr.@50μM
1	20.1	20%
2	0.74	67%
3	0.021	0.60 μM*
4	2.6	21%
5	0.013	1.6μM*
6	24% @ 50 μM	4%
7	0.074	86%
8	2.7	28%
9	59% @ 50 μM	2%
10	0.76	75%
11	7.6	43%
12	50	49%
13	0.34	78%
14	0.028	78%
15	20% @ 5 μM	4%
16	0.008	73%
17	0.003	0.13 μM*
18	0.029	87%
19	5.80	85%

*Indicates IC_{50}

IN VIVO DOG STUDY

Compound 16 was tested in the following *in vivo* dog model to determine its therapeutic efficacy

Surgical Preparation

Adult mongrel dogs of either sex 9-13 kg) were anesthetized with pentobarbital sodium (35 mg/kg, i.v.) and ventilated with room air via an endotracheal tube (12 strokes/min, 25 ml/kg). For arterial pressure determination, the left carotid artery was cannulated with a saline-filled polyethylene catheter (PE-200) and connected to a Statham pressure transducer (P23ID, Oxnard, CA). Mean arterial diastolic blood pressure. Heart rate was monitored using a cardiotachometer (Biotach, Gould

Electronics, Cleveland, OH) triggered from a lead II electrocardiogram generated by limb leads. A jugular vein was cannulated (PE-200) for drug administration. The left femoral artery and the left femoral vein were cannulated with silicon treated (Sigmacote, Sigma Chemical Co., St. Louis, MO), saline filled polyethylene tubing (PE-200) and connected with a 5 cm section of silicon treated tubing (PE-240) to form an extracorporeal arteriovenous shunt (A-V). Shunt patency was monitored using a Doppler flow system (model VF-1, Crystal Biotech Inc., Hopkinton, MA) and proximal to the locus of the shunt. All parameters were monitored continuously on a polygraph recorder (Gould TA-4000, Oxnard CA) at a paper speed of 10 mm/min.

Protocol

On completion of a 15 min post surgical stabilization period, an occlusive thrombus was formed by the introduction of a thrombogenic surface (O braided silk thread, 5 cm in length, Ethicon Inc., Somerville, NJ) into the shunt. Four consecutive 15 min shunt periods were employed with the first consisting of a vehicle infusion followed by increasing concentrations of Compound 16, SC-47643, saline with DMF or saline with citric acid administered as a bolus followed by an infusion beginning 5 min. before insertion of the thrombogenic surface and continued for an additional 15 min. AT the end of each 15 min shunt period the silk was carefully removed and weighed. A fifth shunt immediately following the total cumulative treatment dose was used to assess patency duration as indicated by time to total occlusion. Thrombus weight was calculated by subtracting the weight of the silk prior to placement from the total weight of the silk on removal from the shunt. Arterial blood was withdrawn prior to the first shunt and after each shunt period for determination of whole blood collagen-induced platelet aggregation, thrombin-induced platelet degranulation (platelet ATP release), prothrombin time and platelet count. Template bleeding time was performed beginning 10 min. into each shunt period.

Hematologic Studies

Platelet, WBC and RBC counts and hematocrit determinations were performed on whole blood collected in 2 mg/ml disodium EDTA using a Sysmex™ K1000 (Baxter Laboratories, McGraw Park, IL).

Whole blood platelet aggregation and ATP release were measured using a lumi-aggregation and ATP release were measured using a lumi-aggregometer (Chrono-log, Havertown, PA) by recording the change in impedance (platelet aggregation) and light transmission (ATP-release) through a stirred (1000 rpm) suspension of whole blood maintained at 37 C. Blood samples were collected in 0.01M of sodium citrate and diluted 50% with saline supplemented with 0.5 mM Ca (25 µl of 0.02 M CaCl2 and 20 µl of luciferol (Chrono-log, Havertown, PA). Final volume was 1 ml. Aggregation was induced with collagen (2µg/ml) while in a separate sample, platelet degranulation was monitored using thrombin (0.5 U/ml) (Chrono-log, Havertown, PA) and the changes in impedance and luminescence recorded over 6 min. Prothrombin time (PT) was monitored using a microsample coagulation analyzer (Ciba Corning 512, Corning, NY). Template bleeding time as performed by making an incision into the gum (Surgicutt, ITC Corp, Edison, NJ) and the time to clot formation monitored.

Drugs

Compound 16;1 + 0.03, 3 + 0.1 and 5 + 0.3 mg/kg, i.v. (bolus) + mg/kg/hr,i.v. (infusion) was solubilized in saline + DMF (5%) and serially diluted to achieve appropriate concentrations expressed as parent compound.

Statistical Analysis

The results are shown in Tables2-4. All values are expressed as the mean and standard error of the mean. Statistical significance of the change was assessed based on change from baseline suing analysis of variance and Student's t-test. Differences were considered significant when $P < 0.05$.

[DIP-J Classic の試用モードでダウンロードされました]

TABLE 2

Table 2. Incidence of occlusive thrombus formation during treatment periods and post cumulative dose. The values given are the number of animals per group in which zero shunt blood flow has occurred and the shunt is no longer patent. Dogs are monitored for 60 min during the post treatment recovery period.

Group	Period 1 Control Vehicle	Period 2 Treatment Dose 1	Period 3 Treatment Dose 2	Period 4 Treatment Dose 3	Post Treatment
Control (DMF 5%)	4/4	2/4	1/4	4/4	4/4
CP# 16	4/4	2/4	1/4	0/4	3/4
Control (Citric Acid)		5/5	5/5	5/5	5/5

TABLE 3

Table 3. Effect of Cmpd. #16, and on Thrombus Weight and Bleeding Time

Treatment Group	N	Shunt Period	Thrombus Weight (mg)	Bleeding Time (seconds)
Control DMF 5%	4	Baseline		119±18
	4	1 - Vehicle	58±5	116±27
	4	2 - Dose 1	56±5	120±15
	4	3 - Dose 2	55±6	104±15
	4	4 - Dose 3	63±5	121±27
Compound #16	4	Baseline		101±11
	4	1 - Vehicle	68±5	84±8
	4	2 - Dose 1	52±3	94±7
	4	3 - Dose 2	27±1*	128±14
	4	4 - Dose 3	19±2*	241±23*
Control Citric Acid	5	Baseline		103±14
	5	1 - Vehicle	80±5	80±6
	5	2 - Dose 1	69±4	88±10
	5	3 - Dose 2	65±7	93±18

All values are expressed as mean ± SEM. All parameters were recorded immediately after each shunt period to assess treatment effects.
* Student's t-test vs pre-treatment, $P<0.05$.

TABLE 4

Table 4. Effect of Cmpd #16 on Platelet Count, Gamma Thrombin-Induced Platelet Aggregation, Collagen-Induced Platelet Aggregation, Blood Pressure and Heart Rate

Treatment Group	N	Shunt Period	Platelet Count (X 1000 µl)	G-Thrombin-Induced Plat Agg (%inhib)	Collagen-Induced Plat Agg (%inhib)	Blood Pressure (mmHg)	Heart Rate (beat/min)
Control DMF 5%	4	Baseline	299±25			159±5	168±3
	4	1 - Vehicle	313±20	6±4	3±3	159±6	168±3
	4	2 - Dose 1	273±23	7±7	5±5	162±5	162±5
	4	3 - Dose 2	278±35	8±8	6±6	169±3	160±7
	4	4 - Dose 3	253±15	4±3	2±2	163±5	155±2
	4	30 min post	252±32	5±4	6±4		
	4	60 min post	212±43	7±3	6±4		
Cmpd #16	4	Baseline	409±27			137±13	141±7
	4	1 - Vehicle	380±26	9±6	9±9	141±11	143±6
	4	2 - Dose 1	352±20	8±5	14±3	147±8	146±6
	4	3 - Dose 2	353±22	34±8*	99±1*	141±10	138±4
	4	4 - Dose 3	358±26	72±8*	100±0*	141±9	136±7
	4	30 min post	339±25	21±8	82±13*		
	4	60 min post	360±22	11±5	57±14*		
Control Citric Acid	5	Baseline	317±36	not done		133±9	154±9
	5	1 - Vehicle	315±35		5±3	133±9	154±9
	5	2 - Dose 1	313±34		0±8	131±8	152±8
	5	3 - Dose 2	313±44		18±5	133±8	151±11

All values are expressed as mean ± SEM. All parameters were recorded immediately after each shunt period to assess treatment effects.
* Student's t-test vs pre-treatment, P<0.05.

EXAMPLES

Protected amino acids were purchased from Bachem Bioscience Inc. Use of protected amino N-hydroxysuccinimide esters precludes the use of BOP-Cl (see synthesis of compound **14**). Enantiomerically-enriched nipecotic acid methyl esters were isolated by chiral resolution of racemic material as published (A. M. Akkerman, *Rec. Trav. Chim. Pays-Bas* **1951**, *70*, 899). All other chemicals were purchased from Aldrich Chemical Company, Inc. High field ^{1}H NMR spectra were recorded on a Bruker AC-360 spectrometer at 360 MHz, and coupling constants are given in Herz. Melting points were determined on a Mel-Temp II melting point apparatus and are uncorrected. Microanalyses were performed at Robertson Microlit Laboratories, Inc., Madison, New Jersey or The R. W. Johnson Pharmaceutical Research Institute Analytical Department. Final compounds were purified by recrystallization/precipitation from common organic solvents and/or column chromatography using Merck silica gel-60. Purities were assessed on a combination Beckman/Waters HPLC System and a Phenomenex-Ultracarb 5 ODS(30) column (100x4.6 mm) using an aqueous acetonitrile mobile phase (typically 10% MeCN/90% water). In the Examples and throughout this application, the following abbreviations have the meanings recited hereinafter.

Ac = Acetyl
Bn or Bzl = Benzyl
Boc = t-Butoxycarbonyl
BOP-Cl = Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Cbz = Benzyloxycarbonyl
CP = compound
DIBAL= Diisobutylaluminum hydride
EDC = Ethyl dimethylaminopropylcarbodiimide
EDTA = Ethylenediaminetetraacetic acid
HOBT= Hydroxybenzotriazole
i-Pr = Isopropyl
NMM = N-Methylmorpholine
Nip = Nipecotyl (Unless noted otherwise, racemic at 3-position)
PTSA = p-Toluenesulfonic acid
RT = room temperature
TFA = Trifluoroacetic acid

Example 1- Nα-Boc-D-Lys-S-(+)-Nip-β-Ala-OH (CP #14)

To a mixture of Nα-Boc-D-Lys(Cbz)-OH (2.9 g, 7.74 mmol) and CH_2Cl_2 (80 mL) at 5°C was added BOP-Cl (1.96 g, 7.7 mmol) and NMM (0.83 mL, 7.7 mmol). This mixture was stirred for 30 min, treated with S-(+)-nipecotic acid methyl ester hydrochloride (1.39 g, 7.7 mmol) and NMM (0.83 mL), stirred for 2 h at 5°C, and diluted with sat'd NH_4Cl (50 mL). The organic layer was separated from the aqueous layer, dried with $MgSO_4$, and evaporated to a glassy solid. This solid was purified by flash chromatography (4% $EtOH/CH_2Cl_2$) to afford Nα-Boc-D-Lys(Cbz)-S-(+)-Nip-OMe as a white foam: ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.50 (m, 1 H), 5.09 (s, 2 H), 4.61 (m, 1 H), 3.92 (m, 1 H), 3.66 (s, 3 H), 3.20 (m, 4 H), 2.79 (m, 1 H), 2.51 (m, 1 H), 2.12 (m, 1 H), 1.50-1.80 (m, 10 H), 1.39 (s, 9 H); MS m/e 506 (MH^+).

To a solution of Nα-Boc-D-Lys(Cbz)-S-(+)-Nip-OMe (3.52 g, 7.0 mmol) in THF (25 mL) at RT was added aqueous lithium hydroxide (0.19 g in 15 mL water) dropwise over a 3 min period. This solution was stirred for 6 h and evaporated to give a white foam. This foam was slurried with CH_2Cl_2 (80 mL) at RT and treated sequentially with H-β-Ala-OBn•PTSA (2.43 g, 7.0 mmol), HOBT (5 mg), EDC•HCl (1.98 g, 10.4 mmol), and NMM (0.76 mL, 7.0 mmol). This mixture was stirred for 13 h, diluted with sat'd NH_4Cl (50 mL), and the layers separated. The organic layer was dried with $MgSO_4$ and evaporated to give a white foam. The foam was purified by flash chromatography (3-4% $EtOH/CH_2Cl_2$) to give Nα-Boc-D-Lys(Cbz)-S-(+)-Nip-β-Ala-OBn as a white foam: ^1H NMR ($CDCl_3$) δ 7.35 (m, 10 H), 6.29 (m, 1 H), 5.45 (m, 1 H), 5.12 (s, 2 H), 5.05 (s, 2 H), 5.00 (m, 1 H), 4.55 (m, 1 H), 4.32 (m, 1 H), 3.48 (m, 2 H), 3.19 (m, 4 H), 2.53 (m, 3 H), 2.21 (m, 1 H), 1.84 (m, 1 H), 1.48-1.72 (m, 9 H), 1.42 (s, 9 H); MS m/e 653 (MH^+).

To a solution of Nα-Boc-D-Lys(Cbz)-S-(+)-Nip-β-Ala-OBn (0.80 g, 1.22 mmol) in THF (15 mL) in a Parr bottle under nitrogen atmosphere was added AcOH (5 mL), water (10 mL), and Pd/C (10%, 0.09 g). This mixture was hydrogenated at 50 psi/RT for 21 h, filtered through Celite, and evaporated to *ca.* 5 mL. This solution was treated with Et_2O (60 mL) to give a white ppt which was filtered and lyophilized to afford **14** as colorless flakes: mp 52-60°C; ^1H NMR (DMSO-d_6) δ 7.85 (m, 1 H), 6.83 (d, J=7, 1 H), 4.34 (d, J=12,

1 H), 4.22 (m, 1 H), 3.60 (m, 2 H), 3.41 (m, 2 H), 2.98 (t, J=11, 1 H), 2.88 (m, 1 H), 2.69 (m, 2 H), 2.35 (m, 2 H), 2.12 (m, 1 H), 2.03 (m, 1 H), 1.70 (m, 2 H), 1.4-1.6 (m, 8 H), 1.35 and 1.38 (pr. s, 8.5:1, 9 H), 1.16 (m, 2 H); IR (KBr) 3450-2860, 1709, 1641 cm^{-1}; MS m/e 429 (MH^+); $[\alpha]^{25}_D$ -15.20° (c 0.63, MeOH). Anal. calcd. for $C_{20}H_{36}N_4O_6{\cdot}C_2H_4O_2$ (488.6): C, 54.08; H, 8.25; N, 11.47. Found: C, 54.64; H, 8.26; N, 10.79.

Example 2 - Nα-Boc-L-Lys(Cbz)-Nip-β-Ala-OBn (CP #1)

Compound **1**, prepared starting from Nα-Boc-L-Lys(Cbz)-OH and racemic nipecotic acid methyl ester, as in Example 1, was isolated as a glass: ^1H NMR ($CDCl_3$) δ 7.29 (m, 10 H), 6.51 (m, 1 H), 5.39 (m, 1 H), 5.11 (s, 2 H), 5.06 (s, 2 H), 4.94 (m, 1 H), 4.54 (m, 2 H), 4.18 (m, 1 H), 4.02 (d, J=10, 1 H), 3.61 (m, 1 H), 3.48 (m, 2 H), 3.17 (m, 4 H), 2.54 (m, 3 H), 2.20 (m, 1 H), 1.83 (m, 1 H), 1.67 (m, 2 H), 1.51 (m, 4 H), 1.39 (s, 9 H); MS m/e 653 (MH^+); Anal. calcd. for $C_{35}H_{48}N_4O_8{\cdot}1.5H_2O$ (679.8): C, 61.84; H, 7.56; N, 8.24. Found: C, 62.00; H, 7.25; N, 8.23.

Example 3 - Nα-Boc-L-Lys-Nip-β-Ala--OH (CP #2)

Compound **2**, prepared by hydrogenolysis of **1**, as in Example 1, was isolated as a white foam: ^1H NMR (DMSO-d_6) δ 8.00 (m, 1 H), 7.86 (m, 1 H), 4.29 (m, 2 H), 3.82 (m, 1 H), 3.11 (m, 3 H), 2.70 (m, 2 H), 2.53 (m, 1 H), 2.31 (m, 2 H), 2.17 (m, 2 H), 1.4-1.9 (m, 10 H), 1.34 and 1.36 (pr. s, 1:1, 9 H), 1.23 (m, 2 H); MS m/e 429 (MH^+); $[\alpha]^{25}_D$ +0.85° (c 0.82, MeOH). Anal. calcd. for $C_{20}H_{36}N_4O_6{\cdot}1.5H_2O$ (518.6): C, 53.27; H, 8.16; N, 10.80. Found: C, 53.61; H, 8.18; N, 10.47.

Example 4 - Nα-Boc-D-Lys-Nip-β-Ala--OH (CP #3)

Nα-Boc-D-Lys(Cbz)-Nip-β-Ala-OBn, prepared starting from racemic nipecotic acid methyl ester and Nα-Boc-D-Lys(Cbz)-OH, as in Example 1, was isolated as a white foam: ^1H NMR ($CDCl_3$) δ 7.32 (m, 10 H), 6.59 (m, 1 H), 5.45 (m, 1 H), 5.12 (s, 2 H), 5.07 (s, 2 H), 4.94 (m, 1 H), 4.56 (m, 1 H), 4.12 (m, 1 H), 3.51 (m, 2 H), 3.17 (m, 3 H), 2.57 (m, 2 H), 2.21 (m, 1 H), 1.89 (m, 1 H), 1.45-1.79 (m, 11 H), 1.41 (s, 9 H); MS m/e 653 (MH^+).

Compound 3, prepared by hydrogenolysis of N^{α}-Boc-D-Lys(Cbz)-Nip-β-Ala-OBn, as in Example 1, was isolated as colorless flakes: mp 48-54°C; ^{1}H NMR (DMSO-d_6) δ 7.96 (m, 1 H), 6.82 (m, 1 H), 4.30 (m, 2 H), 3.81 (m, 1 H), 3.12 (m, 4 H), 2.69 (m, 2 H), 2.56 (m, 1 H), 2.33 (m, 2 H), 2.14 (m, 2 H), 1.80 (m, 2 H), 1.4-1.7 (m, 9 H), 1.32 and 1.34 (pr. s, 1:1, 9 H), 1.22 (m, 2 H); IR (KBr) 3580-2770, 1711, 1642 cm^{-1}; MS m/e 429 (MH+); $[\alpha]^{25}_D$ -7.78° (c 1.71, MeOH). Anal. calcd. for $C_{20}H_{36}N_4O_6{\cdot}2C_2H_4O_2{\cdot}0.5H_2O$ (557.6): C, 51.69; H, 8.13; N, 10.05. Found: C, 51.46; H, 8.11; N, 10.10.

Example 5 - N^{α}-Boc-D-Lys-Nip-L-Asp-OMe (CP #18).

N^{α}-Boc-D-Lys(Cbz)-Nip-L-Asp(OBn)-OMe, prepared from H-L-Asp(OBn)-OMe and N^{α}-Boc-D-Lys(Cbz)-Nip-OH, as in Example 1, was isolated as a glass: ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 10 H), 6.84 (m, 1 H), 5.40 (m, 1 H), 5.14 (s, 2 H), 5.09 (s, 2 H), 4.88 (m, 2 H), 4.54 (m, 1 H), 4.30 (m, 1 H), 3.68 (s, 3 H) 3.19 (m, 3 H) 3.03 (m, 1 H), 2.89 (m, 1 H), 2.29 (m, 1 H), 1.43-2.06 (m, 12 H), 1.40 (s, 9 H); MS m/e 711 (MH+).

Compound 18, prepared by hydrogenolysis of N^{α}-Boc-D-Lys(Cbz)-Nip-L-Asp(OBn)-OMe, as in Example 1, was isolated as white foam: ^{1}H NMR (DMSO-d_6) δ 8.33 (m, 1 H), 6.77 (d, J=7, 1 H), 4.32 (m, 3 H), 3.82 (m, 1 H), 3.59 (s, 3 H), 2.96 (m, 2 H), 2.73 (m, 3 H), 2.46 (m, 2 H), 2.34 (m, 1 H), 1.79 (m, 3 H), 1.4-1.7 (m, 8 H), 1.34 and 1.37 (pr. s, 1:1, 9 H), 1.27 (m, 2 H); MS m/e 487 (MH+); $[\alpha]^{25}_D$ -3.57° (c 0.56, MeOH). Anal. calcd. for $C_{22}H_{38}N_4O_8{\cdot}C_2H_4O_2{\cdot}H_2O$ (564.6): C, 51.05; H, 7.85; N, 9.92. Found: C, 50.89; H, 7.88; N, 9.74.

Example 6 - H-L-Lys-Nip-β-Ala-OH (CP #4)

To a solution of compound 2 (0.30 g, 0.70 mmol) in MeOH (10 mL) and water (10 mL) at RT was added HCl (0.50 mL, conc.). This solution was stirred for 1 h and evaporated to *ca.* 2 mL oil. This oil was treated with MeCN (20 mL), filtered, washed with Et_2O (3x20 mL), and dried to afford 4 as a white powder: mp 65-75°C; ^{1}H NMR (DMSO-d_6) δ 8.23 (m, 3 H), 8.06 (m, 3 H), 4.33 (m, 2 H), 3.73 (m, 4 H), 3.25 (m, 2 H), 3.01 (m, 1 H), 2.72 (m, 2 H), 2.44 (m, 1 H), 2.34 (m, 2 H), 1.5-1.8 (m, 6 H), 1.35 (m, 4 H); MS m/e 329 (MH+);

Anal. calcd. for $C_{15}H_{28}N_4O_4{\cdot}2HCl{\cdot}2H_2O$ (437.4): C, 41.19; H, 7.84; N, 12.81. Found: C, 40.97; H, 7.75; N, 12.44.

Example 7 - N-(N^{ε}-Aminocaproyl)-Nip-β-Ala-OH (CP #5)

N-(N^{ε}-Boc-aminocaproyl)-Nip-β-Ala-OBn, prepared starting from racemic nipecotic acid methyl ester and N^{ε}-Boc-aminocaproic acid N-oxysuccinimide ester, as in Example 1, was isolated as an oily solid: ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5 H), 6.51 (m, 1 H), 5.12 (s, 2 H), 4.60 (m, 1 H), 4.39 (m, 1 H), 3.90 (m, 1 H), 3.71 (t, 1 H), 3.52 (m, 3 H), 3.19 (m, 4 H), 2.59 (m, 2 H), 2.30 (m, 2 H), 1.85 (m, 3 H), 1.63 (m, 2 H), 1.51 (m, 2 H), 1.42 (s, 9 H), 1.34 (m, 2 H); MS m/e 504 (MH+).

Compound 5, prepared by hydrogenolysis and then acid hydrolysis of N-(N^{ε}-Boc-aminocaproyl)-Nip-β-Ala-OBn, as in Example 1, was isolated as a glass: ^{1}H NMR (DMSO-d_6) δ 8.18 (t, J=5, 1 H), 8.04 (br. s, 3 H), 4.28 (m, 2 H), 3.78 (m, 2 H), 3.20 (m, 3 H), 2.99 (t, J=12, 1 H), 2.71 (d, J=6, 2 H), 2.39 (m, 2 H), 2.31 (m, 2 H), 2.16 (m, 1 H), 1.79 (m, 1 H), 1.61 (m, 4 H), 1.42 (t, J=6, 2 H), 1.28 (m, 2 H), 1.19 (m, 1 H); MS m/e 314 (MH+); Anal. calcd. for $C_{15}H_{27}N_3O_4{\cdot}2HCl$ (386.3): C, 46.04; H, 7.57; N, 10.88. Found: C, 45.91; H, 7.63; N, 11.17.

Example 8 - N-[3-(4-Piperidinepropionyl)]-Nip-β-Ala-OH (CP #17)

N-[3-(4-Pyridineacryloyl)]-Nip-β-Ala-OBn, prepared starting from 3-(4-pyridine)acrylic acid and racemic nipecotic acid methyl ester, as in Example 1, was isolated as a glass: ^{1}H NMR ($CDCl_3$) δ 8.61 (d, J= 4 Hz, 2 H), 7.52 (d, J= 15 Hz, 1 H), 7.35 (m, 7 H) 7.03 (d, J= 15 Hz, 1 H), 6.58 (m, 1 H), 5.12 (s, 2 H), 4.40 (m, 1 H), 3.89 (m, 1 H), 3.51 (m, 2 H), 3.38 (m, 2 H), 2.60 (t, J= 6 Hz, 2 H), 2.31 (m, 1 H), 1.97 (m, 2 H), 1.74 (m, 1 H), 1.56 (m, 1 H); MS m/e 422 (MH+).

To a solution of N-[3-(4-Pyridineacryloyl)]-Nip-β-Ala-OBn (0.56 g, 1.33 mmol) in EtOH (20 mL) and water (10 mL) under nitrogen atmosphere was added HCl (0.66 mL, 4.0 *M* in dioxane) and platinum^{IV} oxide (0.060 g). This mixture was hydrogenated at 50 psi/RT for 22 h, filtered through Celite, and evaporated to *ca.* 5 mL. This solution was treated with MeCN (30 mL).

filtered, washed with Et_2O (3x20 mL), and dried to give **17** as a pale yellow foam: ^{1}H NMR (DMSO-d_6) δ 9.02 (br. s, 2 H), 8.03 (m, 1 H), 7.46 (m, 1 H), 4.28 (t, J=7, 1 H), 4.11 (m, 1 H), 3.79 (m, 1 H), 3.44 (t, J=7, 1 H), 3.19 (m, 3 H), 3.06 (t, J=12, 1 H), 2.75 (d, J=11, 1 H), 2.53 (m, 1 H), 2.32 (m, 4 H), 2.12 (m, 1 H), 1.77 (m, 2 H), 1.4-1.7 (m, 7 H), 1.27 (m, 2 H), 1.18 (t, J=6, 1 H); MS m/e 340 (MH+); Anal. calcd. for $C_{17}H_{29}N_3O_4$•2HCl (412.4): C, 49.52; H, 7.58; N, 10.19. Found: C, 49.15; H, 7.02; N, 10.48. Accurate protonated mass calcd. for $C_{17}H_{29}N_3O_4$: 340.2236 amu. Found: 340.2245 amu.

Example 9 - N$^\alpha$-Ac-L-Lys-Nip-Gly-OH (CP #6)

N$^\alpha$-Ac-L-Lys(Boc)-Nip-Gly-OBn , prepared starting from N$^\alpha$-Ac-L-Lys(Boc)-OH and racemic nipecotic acid methyl ester (see **14**), was isolated as a glass: ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5 H), 6.97 (m, 1 H), 6.38 (m, 1 H), 5.14 (s, 2 H), 4.70 (m, 1 H), 4.46 (m, 1 H), 4.06 (dd, J= 5, 16 Hz, 2 H), 3.71 (m, 1 H), 3.10 (m, 2 H), 1.99 (s, 3 H), 1.91 (m, 2 H), 1.64 (m, 1 H), 1.41-1.60 (m, 1 H), 1.39 (s, 9 H); MS m/e 547 (MH+).

Compound **6**, prepared by hydrogenolysis of N$^\alpha$-Ac-L-Lys(Boc)-Nip-Gly-OBn, as in Example 1, and then TFA-mediated Boc removal (for method, see M. Bodanszky *The Practice of Peptide Synthesis*, Springer-Verlag: New York, 1984), was isolated as a tan powder: mp 40-55°C; ^{1}H NMR (DMSO-d_6) δ 8.24 (t, J=6, 1 H), 8.03 (d, J=8, 1 H), 7.75 (br. s, 3 H), 4.24 (m, 1 H), 3.72 (t, J=6, 2 H), 3.61 (m, 2 H), 2.72 (m, 2 H), 1.83 (s, 3 H), 1.78 (m, 2 H), 1.63 (m, 2 H), 1.4-1.6 (m, 8 H), 1.28 (m, 4 H); MS m/e 357 (MH+); Anal. calcd. for $C_{16}H_{28}N_4O_5$•$3C_2HF_3O_2$ (698.5): C, 37.83; H, 4.47; N, 8.02. Found: C, 37.91; H, 4.89; N, 8.47.

Example 10 - N$^\alpha$-Ac-L-Lys-Nip-β-Ala-OH (CP #7)

N$^\alpha$-Ac-L-Lys(Boc)-Nip-β-Ala-OBn , prepared starting from N$^\alpha$-Ac-L-Lys(Boc)-OH and racemic nipecotic acid methyl ester as, in Example 1, was isolated as a white foam: ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5 H), 6.53 (m, 2 H), 5.12 (s, 2 H), 4.58 (m, 1 H), 4.10 (m, 1 H), 3.72 (m, 1 H), 3.54 (m, 2 H), 3.11 (m, 3 H), 2.59 (m, 2 H), 2.24 (m, 1 H), 2.01 (s, 3 H), 1.88 (m, 1 H), 1.73 (m, 2 H), 1.52 (m, 8 H), 1.40 (s, 9 H), 1.31 (m, 1 H); MS m/e 561 (MH+).

Compound **7**, prepared by hydrogenolysis of N$^\alpha$-Ac-L-Lys(Boc)-Nip-β-Ala-OBn, as in Example 1, and then acid hydrolysis, as in Example 6, was isolated as a white foam: mp 53-67°C; ^{1}H NMR (DMSO-d_6) δ 8.13 (m, 1 H), 8.00 (m, 1 H), 7.91 (d, J=15, 3 H), 4.64 (m, 1 H), 4.36 (m, 1 H), 3.87 (m, 1 H), 3.66 (m, 2 H), 3.23 (m, 3 H), 2.99 (m, 1 H), 2.68 (m, 2 H), 2.59 (m, 1 H), 2.38 (m, 2 H), 2.11 (m, 1 H), 1.80 (s, 3 H), 1.63 (m, 1 H), 1.4-1.6 (m, 5 H), 1.24 (m, 3 H); MS m/e 371 (MH+); Anal. calcd. for $C_{17}H_{30}N_4O_5$•2HCl•$2H_2O$ (479.4): C, 42.59; H, 7.57; N, 11.69. Found: C, 43.83; H, 7.79; N, 10.91.

Example 11 - N$^\alpha$-Boc-L-Arg-Nip-β-Ala-OH (CP #8)

N$^\alpha$-Boc-L-Arg(Cbz)-Nip-β-Ala-OBn, prepared starting from N$^\alpha$-Boc-L-Arg(Cbz_2)-OSu and racemic nipecotic acid methyl ester, as in Example 1, was isolated as a glass: ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 10 H), 6.69 (m, 1 H), 5.70 (m, 1 H), 5.13 (s, 2 H), 5.03 (s, 2 H), 4.59 (m, 1 H), 4.29 (m, 1 H), 3.52 (m, 2 H), 3.28 (m, 1 H), 3.09 (m, 3 H), 2.60 (m, 3 H), 2.18 (m, 1 H), 1.49-1.90 (m, 11 H), 1.42 (s, 9 H); MS m/e 681 (MH+).

Compound **8**, prepared by hydrogenolysis of N$^\alpha$-Boc-L-Arg(Cbz)-Nip-β-Ala-OBn, as in Example 1, was isolated as a white foam: mp 47-55°C; ^{1}H NMR (DMSO-d_6) δ 9.53 (m, 1 H), 7.85 (m, 2 H), 6.96 (m, 1 H), 4.32 (m, 2 H), 3.84 (m, 1 H), 3.38 (m, 2 H), 3.03 (m, 4 H), 2.20 (m, 3 H), 1.74 (m, 2 H), 1.4-1.7 (m, 8 H), 1.35 (s, 9 H), 1.24 (m, 2 H); MS m/e 457 (MH+); Anal. calcd. for $C_{20}H_{36}N_6O_6$•$1.5C_2H_4O_2$ (546.6): C, 50.54; H, 7.74; N, 15.37. Found: C, 50.24; H, 7.96; N, 15.26.

Example 12 - N$^\alpha$-Boc-L-Lys-Nip-γ-aminobutyric acid (CP #9)

N$^\alpha$-Boc-L-Lys(Cbz)-Nip-γ-aminobutyric acid benzyl ester, prepared starting from N$^\alpha$-Boc-L-Lys(Cbz)-OH and racemic nipecotic acid methyl ester (see **I-1, I-2**), was isolated as a glass: ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 10 H), 6.48 (m, 1 H), 6.16 (m, 1 H), 5.40 (m, 1 H), 5.11 (s, 2 H), 5.08 (s, 2 H), 4.89 (m, 1 H), 4.58 (m, 1 H), 4.07 (m, 1 H), 3.22 (m, 5 H), 2.52 (m, 1 H), 2.40 (m, 2 H), 1.50-2.30 (m, 12 H), 1.42 (s, 9 H), 1.33 (m, 1 H); MS m/e 667 (MH+).
Compound **9**, prepared by hydrogenolysis of N$^\alpha$-Boc-L-Lys(Cbz)-Nip-γ-aminobutyric acid benzyl ester, as in Example 1, was isolated as a white

foam: mp 65-71°C; ^{1}H NMR (DMSO-d_6) δ 8.25 (m, 1 H), 6.87 (m, 1 H), 4.31 (m, 3 H), 3.74 (m, 2 H), 3.15 (m, 2 H), 2.98 (m, 3 H), 2.69 (m, 2 H), 2.10 (m, 3 H), 1.76 (m, 3 H), 1.4-1.7 (m, 9 H), 1.31 (s, 9 H), 1.21 (m, 2 H); MS m/e 443 (MH+); Anal. calcd. for $C_{21}H_{38}N_4O_6{\cdot}2C_2H_4O_2$ (562.7): C, 53.37; H, 8.24; N, 9.96. Found: C, 53.94; H, 8.17; N, 9.70.

Example 13 - H-D-Lys-Nip-β-Ala-OH (CP #10)

Compound **10**, prepared by acid hydrolysis of **3**, as in Example 6, was isolated as a cream powder: mp 108-128°C; ^{1}H NMR (DMSO-d_6) δ 8.28 (m, 3 H), 8.05 (m, 3 H), 4.31 (m, 2 H), 3.84 (m, 2 H), 3.25 (m, 2 H), 3.09 (m, 2 H), 2.72 (m, 3 H), 2.37 (m, 3 H), 1.80 (m, 1 H), 1.5-1.7 (m, 6 H), 1.33 (m, 4 H); MS m/e 329(MH+); Anal. calcd. for $C_{15}H_{28}N_4O_4{\cdot}2HCl{\cdot}C_2H_4O_2$ (461.4): C, 44.26; H, 7.43; N, 12.14. Found: C, 43.98; H, 7.27; N, 12.29.

Example 14 - Nα-Boc-D-Lys-Nip-γ-aminobutyric acid (CP #11)

Nα-Boc-D-Lys(Cbz)-Nip-γ-aminobutyric acid benzyl ester, prepared starting from Nα-Boc-D-Lys(Cbz)-OH and racemic nipecotic acid methyl ester, as in Example 1, was isolated as a glass: ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 10 H), 6.51 (m,1 H), 6.15 (m, 1 H), 5.48 (m, 1 H), 5.10 (s, 1 H), 5.06 (s, 2 H), 4.90 (m, 1 H), 4.55 (m, 1 H), 4.10 (m, 1 H), 3.59 (m, 1 H), 3.23 (m, 5 H), 2.39 (m, 2 H), 2.23 (m, 1 H), 1.84 (m, 2 H), 1.45-1.80 (m, 10 H), 1.38 (s, 9 H), 1.32 (m, 1 H); MS m/e 667 (MH+).

Compound 11, prepared by hydrogenolysis of Nα-Boc-D-Lys(Cbz)-Nip-γ-aminobutyric acid benzyl ester, as in Example 1, was isolated as a tan powder: mp 50-57°C; ^{1}H NMR (DMSO-d_6) δ 7.97 (m, 1 H), 6.91 (m, 1 H), 4.32 (m, 1 H), 4.22 (m, 1 H), 3.82 (m, 1 H), 3.02 (m, 3 H), 2.71 (m, 2 H), 2.52 (m, 1 H), 2.29 (m, 1 H), 2.17 (m, 2 H), 1.84 (m, 5 H), 1.4-1.7 (m, 9 H), 1.33 (s, 9 H), 1.19 (m, 2 H); MS m/e 443 (MH+); Anal. calcd. for $C_{21}H_{38}N_4O_6{\cdot}C_2H_4O_2{\cdot}0.5H_2O$ (571.7): C, 52.53; H, 8.29; N, 9.80. Found: C, 52.91; H, 8.21; N, 9.39.

Example 15 - Nα-Boc-D-Lys-Nip-Gly-OH (CP #12)

Nα-Boc-D-Lys(Cbz)-Nip-Gly-OBn, prepared starting from Nα-Boc-D-Lys(Cbz)-OH and racemic nipecotic acid methyl ester, as in Example 1, was isolated as a glass: ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 10 H), 6.87 (m, 1 H), 5.42 (m, 1 H), 5.19 (s, 2 H), 5.13 (s, 2 H), 4.93 (m, 1 H), 4.60 (m, 1 H), 4.20 (m, 1 H), 4.09 (m, 1 H), 3.40-4.00 (m, 3 H), 3.21 (m, 2 H), 2.61 (m, 1 H), 2.43 (m, 1 H), 1.45-2.20 (m, 10 H), 1.39 (s, 9 H); MS m/e 639 (MH+).

Compound 12, prepared by hydrogenolysis of Nα-Boc-D-Lys(Cbz)-Nip-Gly-OBn, as in Example 1, was isolated as white flakes: mp 66-80°C; ^{1}H NMR (DMSO-d_6) δ 7.82 (m, 1 H), 6.81 (d, J=7, 1 H), 4.34 (m, 2 H), 4.09 (m, 1 H), 3.77 (m, 1 H), 3.48 (m, 1 H), 3.16 (m, 2 H), 2.70 (m, 3 H), 2.44 (m, 2 H), 2.28 (m, 1 H), 1.78 (m, 2 H), 1.4-1.7 (m, 8 H), 1.32 and 1.35 (pr. s, 1:1, 9 H), 1.23 (m, 2 H); MS m/e 415 (MH+); Anal. calcd. for $C_{19}H_{34}N_4O_6{\cdot}2C_2H_4O_2$ (534.6): C, 51.67; H, 7.92; N, 10.48. Found: C, 52.06; H, 8.33; N, 10.19.

Example 16 - Nα-Ac-D-Lys-Nip-β-Ala-OH (CP #13)

Nα-Ac-D-Lys(Cbz)-Nip-β-Ala-OBn , prepared starting from Nα-Ac-D-Lys(Cbz)-OH and racemic nipecotic acid methyl ester, as in Example 1, was isolated as a glass: ^{1}H NMR ($CDCl_3$) δ 7.32 (m,10 H), 6.54 (m, 1 H), 6.36 (m, 1 H), 5.10 (s, 2 H), 5.02 (s, 2 H), 4.89 (m, 2 H), 4.48 (m, 1 H), 4.04 (m, 1 H), 3.69 (m, 1 H), 3.52 (m, 2 H), 3.17 (m, 3 H), 2.57 (m, 2 H), 2.20 (m, 1 H), 1.98 (s, 3 H), 1.25-1.90 (m, 10 H); MS m/e 595 (MH+).

Compound 13, prepared by hydrogenolysis of Nα-Ac-D-Lys(Cbz)-Nip-β-Ala-OBn, as in Example 1, was isolated as a glass: mp 46-59°C; ^{1}H NMR (DMSO-d_6) δ 8.11 (m, 3 H), 4.70 (m, 1 H), 4.33 (m, 1 H), 3.74 (m, 1 H), 3.38 (m, 1 H), 3.19 (m, 4 H), 3.00 (m, 1 H), 2.68 (m, 2 H), 2.21 (m, 4 H), 1.82 (s, 3 H), 1.76 (m, 2 H), 1.4-1.7 (m, 7 H), 1.24 (m, 2 H); MS m/e 371 (MH+); Anal. calcd. for $C_{17}H_{30}N_4O_5{\cdot}2.5C_2H_4O_2$ (520.6): C, 50.76; H, 7.74; N, 10.76. Found: C, 51.12; H, 8.04; N, 10.75.

Example 17 - Nα-Boc-L-Lys(i-Pr)-Nip-β-Ala-OH (CP #15)

Nα-Boc-L-Lys(i-Pr)(Cbz)-Nip-β-Ala-OBn , prepared starting from Nα-Boc-L-Lys(i-Pr)(Cbz)-OH and racemic nipecotic acid methyl ester, as in Example 1, was isolated as a glass: ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 10 H), 6.58 (m, 1 H), 5.10 (s, 2 H), 5.08 (s, 2 H), 4.55 (m, 1 H), 4.21 (m, 1 H), 3.73 (m, 1 H), 3.50 (m, 2 H), 3.17 (m, 3 H), 2.55 (m, 2 H), 2.18 (m, 1 H), 1.50-2.00 (m, 13 H), 1.40 (s, 9 H), 1.13 (d, J= 8 Hz, 6 H); MS m/e 695 (MH^+).

Compound **15**, prepared by hydrogenolysis of Nα-Boc-L-Lys(i-Pr)(Cbz)-Nip-β-Ala-OBn, as in Example 1, was isolated as white flakes: mp 90-123°C; ^{1}H NMR (DMSO-d_6) δ 7.93 (m, 1 H), 6.81 (d, J=7, 1 H), 4.36 (m, 1 H), 4.24 (m, 1 H), 3.60 (m, 1 H), 3.37 (m, 1 H), 3.10 (m, 1 H), 2.91 (m, 3 H), 2.62 (m, 3 H), 2.39 (m, 2 H), 2.14 (m, 1 H), 2.05 (m, 1 H), 1.4-1.8 (m, 9 H), 1.34 and 1.37 (pr. s, 1:1, 9 H), 1.26 (m, 3 H), 1.13 (d, J=5, 6 H); IR (KBr) 3500-2830, 1704, 1638 cm^{-1}; MS m/e 471 (MH^+); Anal. calcd. for $C_{23}H_{42}N_4O_6 \cdot 2C_2H_4O_2$ (590.7): C, 54.90; H, 8.53; N, 9.48. Found: C, 54.67; H, 8.65; N, 9.79.

Example 18 - Nα-Boc-D-Lys-R-(-)-Nip-β-Ala-OH (CP #16)

Compound **16**, prepared starting from Nα-Boc-D-Lys(Cbz)-OH and R-(-)-nipecotic acid methyl ester, as in Example 1, was isolated as a colorless flakes: mp 42-51°C; ^{1}H NMR (DMSO-d_6) δ 7.95 (m, 1 H), 6.82 (d, J=7, 1 H), 4.33 (m, 1 H), 4.19 (m, 1 H), 3.79 (m, 1 H), 3.25 (m, 1 H), 3.04 (t, J=10, 2 H), 2.69 (m, 2 H), 2.34 (m, 1 H), 2.21 (m, 1 H), 2.14 (m, 2 H), 1.78 (m, 2 H), 1.71 (m, 2 H), 1.4-1.6 (m, 9 H), 1.34 and 1.38 (pr. s, 1:8, 9 H), 1.20 (m, 2 H); MS m/e 429 (MH^+). Anal. calcd. for $C_{20}H_{36}N_4O_4 \cdot 2.5\ C_2H_4O_2$ (578.7): C, 51.89; H, 8.01; N, 9.68. Found: C, 52.05; H, 7.98; N, 9.58.

Example 19 - N-(Nε-Aminocaproyl)-3-piperidinemethylaminopropionic acid (CP #19)

To a solution of N-(Nε-Boc-aminocaproyl)-nipecotic acid (3.1 g, 9.0 mmol) and THF (50 mL) was added 1,1-carbonyldiimidazole (1.45 g, 9.0 mmol). This solution was stirred for 1 h, cooled to -10°C, treated with DIBAL (36.0 mL, 1.0 *M* in toluene) dropwise over a 20 min period, and stirred for an additional 2 h. This solution was treated with aqueous citric acid (5.0 g in 40 mL water),

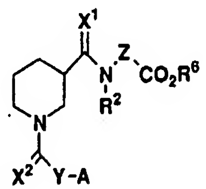
diluted with $CHCl_3$ (200 mL), and the resultant layers were separated. The aqueous layer was extracted with $CHCl_3$ (100 mL), and the combined organic layers were dried, evaporated, and purified by flash chromatography (4% $EtOH/CH_2Cl_2$) to afford N-(Nε-Boc-aminocaproyl)piperidine-3-carboxaldehyde as a glass: ^{1}H NMR ($CDCl_3$) δ 9.65 (d, J= 8 Hz, 1 H), 4.58 (m, 1 H), 4.10 (m, 1 H), 3.65 (m, 1 H), 3.45 (m, 1 H), 3.22 (m, 1 H), 3.14 (m, 2 H), 2.46 (m, 2 H), 2.33 (t, J= 7 Hz, 1 H), 2.09 (m, 1 H), 1.5-1.8 (m, 7 H), 1.39 (s, 9 H), 1.33 (m, 2 H); MS m/e 327 (MH^+).

To a solution of N-(Nε-Boc-aminocaproyl)piperidine-3-carboxaldehyde (0.69 g, 2.12 mmol) in MeOH (10 mL) at RT was added H-β-Ala-OBn•PTSA (0.74 g, 2.12 mmol) and $NaCNBH_3$ (0.13 g, 2.12 mmol). This mixture was stirred for 2.5 h and evaporated to a white solid. This solid was partitioned between sat'd $NaHCO_3$ (10 mL) and CH_2Cl_2 (50 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x50 mL), and the combined organic layers were dried, evaporated, and purified by flash chromatography (0.5% NH_4OH/4-10% $EtOH/CH_2Cl_2$) to give N-(Nε-Boc-aminocaproyl)-3-piperidinemethylaminopropionic acid benzyl ester as a glass: ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5 H), 5.13 (s, 2 H), 4.61 (m, 1 H), 4.28 (m, 1 H), 3.70 (m, 1 H), 3.11 (m, 3 H), 2.85 (m, 3 H), 2.53 (m, 4 H), 2.31 (t, J= 7 Hz, 2 H), 1.5-1.9 (m, 8 H), 1.42 (s, 9 H), 1.29 (m, 3 H), 0.89 (m, 1 H); MS m/e 490 (MH^+).

To a solution of N-(Nε-Boc-aminocaproyl)-3-piperidinemethylaminopropionic acid benzyl ester (0.28 g, 0.57 mmol) and THF (10 mL) at RT was added aqueous HCl (3.4 mL, 1.0 *N*). This mixture was stirred for 22 h, evaporated to a glassy solid, triturated with Et_2O (3x25 mL), and dried to give a white powder. This powder was dissolved in THF (5 mL) and water (10 mL), transferred t a Parr bottle under nitrogen atmosphere, and treated with Pd/C (0.04 g, 10%). This mixture was hydrogenated at 50 psi/RT for 20 h, filtered through Celite, and evaporated to ca. 5 mL. This solution was treated with MeCN (25 mL), filtered, washed with Et_2O (2x25 mL), and dried to give **19** as a colorless glass (HPLC purity> 95%): mp 65-74°C; ^{1}H NMR (DMSO-d_6) δ 9.31 (m, 2 H), 8.12 (br. s, 3 H), 4.18 (m, 2 H), 3.70 (m, 1 H), 3.04 (m, 2 H), 2.67 (m, 5 H), 2.51 (m, 1 H), 2.35 (m, 3 H), 1.87 (m, 2 H), 1.58 (m, 4 H), 1.42 (m, 2 H), 1.30 (m, 4 H); MS m/e 300 (MH^+). Accurate protonated mass calcd. for $C_{15}H_{29}N_3O_3 \cdot 2HCl$ (372.3): 300.2287 amu. Found: 300.2306 amu.

WE CLAIM:

1. A compound represented by the general formula (I):



wherein X^1 and X^2 are the same or different and selected from either of H_2 or O;

wherein Y is selected from any of $(CH_2)_m$, $CH(NHCOR^3)(CH_2)_m$ or $CH((NH_2)CH_2)_m$;

wherein A is selected from any of NHR^1, $C(:NH)NH_2$ or a cycloalkyl ring containing a nitrogen therein which ring is selected from any of piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, pyrrolidin-2-yl and pyrrolidin-3-yl;

wherein Z is selected from any of $(CH_2)_n$ or $CH(CO_2R^4)(CH_2)_n$;

wherein R^1 is selected from any of H, alkyl, or $CH(NH)NH_2$;

wherein R^2 is selected from any of H or alkyl;

wherein R^3 is selected from any of alkoxy or alkyl;

wherein R^4 is alkyl or arylalkyl;

wherein R^6 is H, alkyl or arylalkyl;

wherein m is the integer 0, 1, 2, or 3;

wherein n is the integer 0, 1, or 2;

or the enantiomer or the pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein Z is $(CH_2)_2$.

3. The compound of claim 1, wherein R^1 is H.

4. The compound of claim 1, wherein R^2 is H.

5. The compound of claim 1, whererin R^3 is t-butoxy.

6. The compound of claim 1, wherein R^4 is methyl.

7. The compound of claim 1, wherein Z is $CH(CO_2R^4)(CH_2)$.

8. The compound of claim 1, selected from any of:

Nα-Boc-L-Lys(Cbz)-Nip-β-Ala-OBn (CP #1);
Nα-Boc-L-Lys-Nip-β-Ala-OH (CP #2);
Nα-Boc-D-Lys-Nip-β-Ala-OH (CP #3);
H-L-Lys-Nip-β-Ala-OH (CP #4);
N-(Nε-Aminocaproyl)-Nip-β-Ala-OH (CP #5);
Nα-Ac-L-Lys-Nip-Gly-OH (CP #6);
Nα-Ac-L-Lys-Nip-β-Ala-OH (CP #7);
Nα-Boc-L-Arg-Nip-β-Ala-OH (CP #8);
Nα-Boc-L-Lys-Nip-γ-aminobutyric acid (CP #9);
H-D-Lys-Nip-β-Ala-OH (CP #10);
Nα-Boc-D-Lys-Nip-γ-aminobutyric acid (CP #11);
Nα-Boc-D-Lys-Nip-Gly-OH (CP #12);
Nα-Ac-D-Lys-Nip-β-Ala-OH (CP #13);
Nα-Boc-D-Lys-S-(+)-Nip-β-Ala-OH (CP #14);
Nα-Boc-L-Lys(i-Pr)-Nip-β-Ala-OH (CP #15);
Nα-Boc-D-Lys-R-(-)-Nip-β-Ala-OH (CP #16);
N-[3-(4-Piperidinepropionyl)]-Nip-β-Ala-OH (CP #17);
Nα-Boc-D-Lys-Nip-L-Asp-OMe (CP #18); or
N-(Nε-Aminocaproyl)-3-piperidinemethylaminopropionic acid (CP #19)